In-vivo angular double-PFG MRI of the human brain

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Introduction: The double-pulsed field gradient (double-PFG) sequence is a recent and exciting development in diffusion MRI (dMRI) that allows for new ways to probe tissue microstructure. It uses two pairs of diffusion-sensitizing gradients instead of the current standard for diffusion MRI, which comprises a single gradient pair (single PFG). Experimental results demonstrate that angular double-PFG analysis alleviates the demand for strong gradients for microstructure determination [Ozarslan08, Koch08, Shemesh09], and that estimation of novel features of tissue that displays a microscopic anisotropy may be possible using clinical scanners. We here present new data supporting this claim.

Aims: (1) To verify the feasibility to perform *in vivo* angular double-PFG MRI of the human brain on a clinical whole-body MRI scanner; (2) to verify that the angular double-PFG signatures previously obtained in rat brain [Shemesh11] can be obtained in an *in vivo* scan of the human brain.

Theory and method: Images were acquired using a stimulated-echo based double-PFG sequence at a clinical MRI scanner (Philips Achieva 3T). Imaging parameters were: TE_1 = 39 ms, TE_2 = 55 ms, TR = 2500 ms, voxel size = 3×3×3 mm^3. The diffusion encoding of the first gradient pair was performed in the x-direction, $\mathbf{n}_1 = [1, 0, 0]$, while the direction of the second gradient pair was varied within the imaging plane, according to $\mathbf{n}_2 = [\cos\theta, \sin\theta, 0]$, with θ varied between 0 and 2π in 30 linearly spaced steps. The b-value of each gradient pair was 500 s/mm^2, yielding a total b-value of 1000 s/mm^2. The mixing time was approximately 35 ms.

For each voxel in the images acquired, the following phenomenological model was fitted to the data:

$$S(\theta) = A \sin^2(\theta + \psi) + B + C \cdot \theta \qquad (1)$$

with A, B, C and ψ as free variables. The last term corrected for a signal drift in frontal parts of the brain that probably results from a movement artifact. The model is similar to that presented by Shemesh *et al.* [Shemesh11, presentation].

In order to understand what to expect from the phenomenological model, consider a voxel containing a distribution $p(\mathbf{u})$ of microscopic domains in which the diffusion is anisotropic and described by the diffusion tensor $\mathbf{D}(\mathbf{u}) = \mathbf{u}^T\mathbf{u}(AD - RD) + \mathbf{I} \cdot RD$, where AD and RD are the axial and radial diffusivities in the microscopic domain, and $\mathbf{u}$ is a row-vector. Under these assumptions, the expected signal from the double-PFG experiment is

$$S_d(\mathbf{n}_1, \mathbf{n}_2) = \int p(\mathbf{u}) \exp\left(-b\mathbf{n}_1 D(\mathbf{u}) \mathbf{n}_1^T\right) \cdot \exp\left(-t_d \mathbf{n}_2 D(\mathbf{u}) \mathbf{n}_2^T\right) d\mathbf{u} \qquad (2)$$

whereas the expected signals from two single-PFG experiment that are multiplied with each other is

$$S_s(\mathbf{n}_1, \mathbf{n}_2) = \prod_{i=1}^{2} \left(\int p(\mathbf{u}) \exp\left(-b\mathbf{n}_i D(\mathbf{u}) \mathbf{n}_i^T\right) d\mathbf{u} \right) \qquad (3)$$

Limiting the analysis to a two-dimensional case, assuming $RD = 0$, and that domains are oriented in a single direction only, i.e. $p(\mathbf{u}) = \delta(\mathbf{v})$, with $\mathbf{v} = [\sin\varphi, \cos\varphi]$, both Eq. 2 and 3 simplify to $S(\theta, \varphi) = \exp(-b\,AD) \cdot \exp(\sin^2(\theta+\varphi) + \sin^2(\varphi))$, with $\mathbf{n}_1$ and $\mathbf{n}_2$ defined as stated above. We thus expect φ in the phenomenological model to reflect the angular deviation of the coherent fibre bundles from $\mathbf{n}_1$. In cases where $p(\mathbf{u})$ contains an orientation dispersion, however, we expect the outcome of Eq. 2 and 3 to differ. That could allow for the orientation dispersion to be estimated from the difference between single-PFG and double-PFG measurements, although such an investigation was outside the scope of the present study.

Results: Maps of the amplitude A and phase φ are shown in Fig. 1. High values of A were found in the white matter, except in regions where fiber bundles are known to cross. The phase map was generally smooth in white matter regions, but had a less consistent appearance in gray matter regions. The slope metric, C, was generally close to zero, except in frontal parts of the brain (data not shown). The model in Eq. 1 fitted well to the data, as shown in Fig. 2.

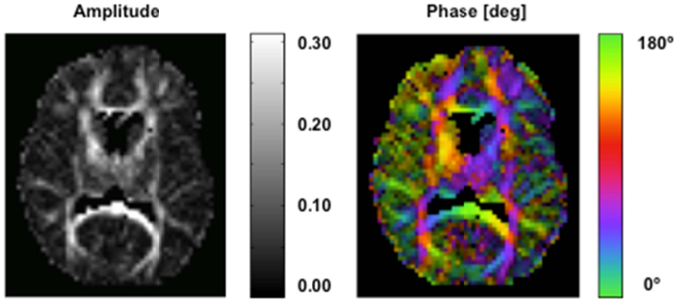

Fig. 1 (above): Parametric maps of the amplitude A and phase φ in Eq. 1. The amplitude showed high values in white matter structures, except in areas where fiber bundles cross.

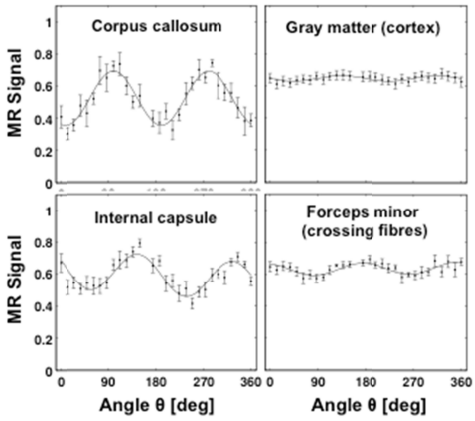

Fig. 2 (right): MR signal versus the angle between the gradients. The signal values agreed well with the model. Error bars show the signal standard error within the ROI.

Discussion and conclusions: The advantage of the double-PFG sequence is that it provides previously unavailable diffusion properties that can be mapped into families of new types of geometric and tissue specific parameters [Ozarslan09], and that it alleviates the requirement for high-strength gradients for microstructure determination, since the theory supports that it can be performed at the "low b" or "low q" values [Ozarslan08, Shemesh09] available on clinical scanners. The presented work shows that it is possible to perform *in vivo* double-PFG imaging of the human brain with a good SNR, indicating that the new the microstructural contrasts from double-PFG can be made available to studies of clinical populations.

References: [Ozarslan08] Özarslan E, Basser PJ. The Journal of Chemical Physics, 2008;128:154511-11. [Koch08] Koch MA and Finsterbusch J, Magn. Reson. Med. 2008, 60:90. [Shemesh09] Shemesh N, Özarslan E, Basser PJ, Cohen Y. Journal of Magnetic Resonance 2009;198:15–23. [Ozarslan09] Evren Özarslan, Journal of Magnetic Resonance 2009;199:56-67. [Shemesh11] Shemesh N, Sadan O, Offen D, Cohen Y. Proc Intl Soc Magn Reson Med 2011#98.